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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,075	06/01/2005	Maria Kebeler	12810-00091-US	2104

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,075	KEBELER ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1/05,8/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Sequence Rules

The Sequence Listing filed 8/6/07 is acceptable and has been entered.

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it uses legal phraseology such as “said host cells” and “said nucleic acid sequence”, etc. Correction is required. See MPEP § 608.01(b).

35 USC 103(a) Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al. in view of Moralejo et al.

Applicants claim a method for expressing nucleic acid sequences in prokaryotic host cells (such as *E. coli*), where:

a) at least one DNA construct which is capable of episomal replication in said host cells and which comprises a nucleic acid sequence to be expressed under the transcriptional control of an L-rhamnose-inducible promoter, where said promoter is heterologous with regard to said nucleic acid sequence, is introduced into said host cells and

b) prokaryotic host cells which comprise said DNA construct in episomal form are selected and

c) the expression of said nucleic acid sequence is induced by addition of L-rhamnose to a culture of said selected host cells, wherein the prokaryotic host cell is at least deficient with regard to L-rhamnose isomerase.

Wilms et al. (cited by applicants, Biotech. Bioengeer., 2001, Vol. 73, No. 2, pp. 95-103, see whole article, particularly the Abstract, pp. 97-98, 100) teaches a method for expressing nucleic acid sequences in *E. coli* wherein circular episomal plasmids (pAW178, pBW24, less than 100K in size) are used to express a heterologous polypeptide (the enzyme L-*N*-carbamoylase) wherein the sequence encoding the polypeptide is operably linked to the *E. coli* rha_{BAD} promoter which comprises at least one RhaS binding site which is a functional equivalent of SEQ ID NO:5 and expression of the heterologous polypeptide is induced by addition of L-rhamnose to the culture. The host cells have the RhaB gene inactivated and the cells are used to produce a heterologous polypeptide enzyme, L-*N*-carbamoylase. Wilms et al. teaches that inactivation of the RhaB gene was desirable because it reduced consumption of the expensive inducer L-rhamnose. Wilms et al. does not teach inactivation of the L-rhamnose isomerase gene in the host cell.

Moralejo et al. (cited by applicants, J. Bacteriol., 1993, Vol. 175, No. 17, pp. 5585-5594, see whole article, particularly Fig. 1, first full paragraph on p. 5591) teaches the gene cluster encoding the enzymes for L-Rhamnose metabolism in *E. coli*. Moralejo et al. teaches the gene encoding the rhamnose isomerase (RhaA) (functional equivalent of SEQ ID NO:9) and that inactivation of this gene would be expected to block any catabolism of L-rhamnose.

The claimed invention is essentially described by Wilms et al. The only difference involves the inactivation of the host cellular RhaA gene. Wilms et al. inactivated the host cellular RhaB gene in order to reduce the consumption of the

expensive inducer L-rhamnose whereby the normal rhamnose catabolism pathway in the cell is inhibited. The ordinary skilled artisan, seeking to develop a method for production of heterologous polypeptides in prokaryotic cells, would have been motivated to use the method disclosed by Wilms et al. and modify said method by inactivating the RhaA gene because Moralejo et al. teaches **that inactivation of the RhaA gene would be expected to block <u>any catabolism</u> of L-rhamnose** in the cell, thereby greatly reducing the amount of the expensive inducer L-rhamnose needed to induce the expression of the recombinant polypeptide. It would have been obvious for the ordinary skilled artisan to do this because inactivation of the RhaA gene in the host cells would greatly reduce the amount of L-rhamnose needed to induce the recombinant expression of the polypeptide of interest in the cell and thereby reduce the cost of using the system exemplified by Wilms et al. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilms et al. in view of Moralejo et al. and Israelsen et al.

Applicants invention is as recited in the above 35 USC 103(a) rejection. In addition, applicants recite that the nucleic acid sequence encoding the recombinant protein is selected from the group consisting of chymosines, proteases, polymerasen, saccharidases, dehydrogenases, nucleases, glucanases, glucose oxidases, a-

amylases, oxidoreductases, peroxidases, laccases, xylanases, phytases, cellulases, collagenases, hemicellulases, lipases, lactases, pectinases, amyloglucosidases, glucoamylases, pullulanases, glucose isomerases, nitrilases, esterases, nitrile hydratases, amidases, oxygenases, oxynitrilases, lyases, lactonases, carboxylases, collagenases, cellulases, serum albumins, factor VII, factor VIII, factor IX, factor X, tissue plasminogen factors, protein C, von Willebrand factors, antithrombins, erythropoietins, colony-stimulating factors, cytokines, interleukins, insulins, integrins, addressins, selectins, antibodies, antibody fragments, structural proteins, collagen, fibroins, elastins, tubulins, actins, myosins, growth factors, cell-cycle proteins, vaccines, fibrinogens and thrombins.

Wilms et al. and Moralejo et al. are applied as in the above 35 USC 1034(a) rejection. WIlms et al. and Moralejo et al. do not recite the recombinant protein as being one of the members of the Markush group recited in claim 12.

Israelsen et al. (US Patent 5,837,509, see whole document, particularly column 13) recites the well known and widely practiced use of recombinant bacteria to express recombinant proteins of interest such as proteases, nucleases, lipases, etc. It is noted that the Israelsen et al. reference is one among thousands of references reciting the use of recombinant bacteria to express genes of interest.

The ordinary skilled artisan, seeking to choose proteins of interest to express using the expression system disclosed by Wilms et al. and Moralejo et al., would have been motivated to choose proteins such as proteases, nucleases, lipases, etc. because Israelsen et al. teaches that recombinant bacteria can be used as hosts for expression

of such proteins. It would have been obvious for the ordinary skilled artisan to do this because recombinant bacteria had been used for decades to express hundreds of different proteins of interest, as exemplified by Israelsen et al. It is further noted that any of the proteins recited in claim 12, would have been obvious to the ordinary skilled artisan as recombinant bacteria had been used to express any/all of the recited proteins. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 12, 2008

/David Guzo/
Primary Examiner
Art Unit 1636